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A Pharmacological Comparison of the Receptors Mediating Contractile Responses to 5-Hydroxytryptamine in the Rat Isolated Caudal Artery and Fundic Strip

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Abstract—Contractile responses to 5-hydroxytryptamine (5-HT) and to a number of 5-HT-receptor agonists have been compared on the rat isolated caudal artery and stomach fundic strip. On the caudal artery, 5-HT was the most potent agonist tested. The 5-HT_1-like agonist, 5-carboxamidotryptamine (5-CT), was less potent than 5-HT and produced a lower maximum response. 8-Hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT) and RU24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)1H indole) were inactive as agonists and 8-OH-DPAT was not an antagonist. Ketanserin, ICI 169,369 (2-(2-dimethylaminoethylthio)-3-phenylquinoline hydrochloride) and ICI 170,809 (2-(2-dimethylamino-2-methylpropylthio)-3-phenylquinoline hydrochloride) were competitive antagonists of 5-HT on this preparation, indicating that 5-HT is acting via 5-HT_2 receptors. In contrast, all the agonists produced contractions of the fundic strip (rank order of potency, 5-HT = 5-CT > RU24969 > 8-OH-DPAT). The maximum response to RU24969 was significantly lower than the maximum responses to the other agonists. Ketanserin was only a weak antagonist of 5-HT in the fundic strip, demonstrating that 5-HT_2 receptors were not involved, but ICI 169,369 and ICI 170,809 were non-surmountable antagonists of 5-HT responses, as were methysergide and methiothepin. Since ICI 169,369 and ICI 170,809 are devoid of activity at 5-HT_3 and 5-HT_4 receptors, then these two subtypes would not appear to be implicated, a view that was confirmed in the case of 5-HT_3 receptors by experiments using ondansetron. Since radioligand binding studies have shown that ICI 169,369 and ICI 170,809 have high affinity for 5-HT_{1C} sites, α-methyl-5-HT, an agonist claimed to be selective for 5-HT_{1C} and 5-HT_2 receptors, was also tested on the fundic strip in the presence of ketanserin. This compound acted as an agonist and was antagonized in a competitive manner by ICI 170,809. Therefore, these results suggest that the receptors mediating contractile responses to 5-HT in the rat fundic strip are more similar to the 5-HT_{1C} subtype than any of the other subtypes that have been described previously.

The original classification of 5-HT receptors into the M and D subtypes (Gaddum & Picarelli 1957) was extended in 1979 when two distinct binding sites for 5-HT were identified in rat brain (Peroutka & Snyder 1979). These sites were later demonstrated to fulfil the criteria for receptors and further studies led to the conclusion that there were multiple receptor subtypes for 5-HT (Bradley et al 1986). Those authors concluded that there were three main types of 5-HT receptor, two of which had been well characterized pharmacologically, using selective antagonists. These were named 5-HT_2 and 5-HT_3. A number of other actions of 5-HT were regarded as being mediated via receptors distinct from 5-HT_2 or 5-HT_3 receptors and this heterogeneous group was tentatively classified as 5-HT_1-like. The 5-HT_1-like receptor incorporated four distinct subtypes designated 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_{1D} (Fozard 1987). Whilst the identity of the receptor mediating 5-HT-induced contractions of the rat caudal artery to 5-HT is generally accepted to be 5-HT_2 (Van Neuten et al 1981), it is still unclear which receptor subtype mediates the response to 5-HT in the rat fundic strip preparation. The receptor would not appear to be of the 5-HT_2 type since it is insensitive to 5-HT_2-receptor antagonists (Cohen & Wittenhauer 1985; Cohen & Colbert 1986; Cohen & Fludinski 1987; Clineschmidt et al 1985). One paper considered that the receptor involved was of the 5-HT_{1C} subtype (Buchheit et al 1986), but recent studies have cast doubt on this supposition (Baez et al 1990). We have therefore attempted to provide more information on this problem by comparing the pharmacology of the fundic strip with that of the caudal artery. To aid in this analysis we have used the selective 5-HT_2 antagonist ketanserin that has a greater potency for 5-HT_2 receptors than for 5-HT_{1C} receptors and compared its effects with agents which have affinity for both 5-HT_2 and 5-HT_{1C} sites (Major et al unpublished data).

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Materials and Methods

Drugs

Atropine sulphate and 5-hydroxytryptamine creatinine sulphate (5-HT) were obtained from Sigma Chemicals Ltd (Dorset, UK), 5-carboxamidotryptamine (5-CT) and ondansetron from Glaxo plc (Greenford, UK), ketanserin from Janssen Pharmaceuticals (Beerse, Belgium), methiothepin from Hoffman La Roche (Basel, Switzerland) and methysergide from Sandoz Ltd, (Basel, Switzerland). ICI 169,369 and ICI 170,809 (2-(2-dimethylaminoethylthio)-3-phenylquinoline hydrochloride and 2-(2-dimethylamino-2-methylpropylthio)-3-phenylquinoline hydrochloride, respectively), α-methyl-5HT, 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)-tetralin) and RU24969 (5-methoxy-3-(1,2,3,6,-tetrahydropyridin-4-yl)1H indole succinate were synthesized by R Pearce, Chemistry II Department, ICI (Macclesfield, UK).

Cyanopindolol was kindly donated by Dr J. R. Fozard, Sandoz Ltd.

Animals

Alderley Park male rats, 250–350 g, were killed by cervical dislocation and exsanguination, and the stomach and caudal artery removed for further dissection.

Rat fundic strip

The fundic region of the rat stomach was dissected away from the pyloric region whilst immersed in Krebs–Henseleit solution. The fundus was then cut into strips approximately 2 cm long and 3 mm wide. The strips were mounted in organ baths containing Krebs–Henseleit solution gassed with 95% O_2–5% CO_2, for isotonic recording of tension changes, at a resting tension of 1·0 g. Following a 30-min equilibration period, concentration-effect curves to an agonist were obtained with a 5-min washout period between each addition of agonist drug. When antagonist drugs were present in the Krebs–Henseleit solution, a 30-min equilibration period was allowed before addition of an agonist. Atropine (1 μM) was present throughout the experiment.

Rat caudal artery

The artery was cut helically into strips approximately 2 cm long and 2 mm wide. The strips were then set up in organ baths under the same conditons as the fundic strip, except that the resting tension was 0·5 g, no atropine was present and concentration-effect curves were obtained by cumulative addition of agonists.

Experimental design

The agonist effects of 5-HT, 5-CT, 8-OH-DPAT and RU-24969 were assessed by constructing concentration-effect curves to each agonist in a randomized fashion. All responses were compared with the maximal effect produced by 5-HT and plotted as a percentage of that maximal effect. The potency of each agonist relative to 5-HT was assessed by comparing EC50 values (EC50 being the concentration of an agonist producing a response that is 50% of its own maximum effect).

The effects of antagonists were evaluated by comparing concentration-effect curves in the absence of an antagonist to that obtained following a 30-min incubation with the antagonist. Where appropriate, agonist EC50 values were compared in the absence and presence of antagonist and a concentration ratio calculated.

The statistical significance of any effects were determined using Student's *t*-test with a significant difference being accepted when $P < 0{\cdot}05$. All data were obtained from at least four experiments using tissues taken from at least four different rats in each case.

Results

The effects of the various 5-HT agonists on the rat caudal artery preparation are shown in Fig. 1. 5-HT and 5-CT produced concentration-related contractions of the tissue. 5-CT (EC50 $13 \pm 0{\cdot}8$ μM) was approximately one-fifteenth as potent as 5-HT (EC50 $0{\cdot}85 \pm 0{\cdot}02$ μM). Neither 8-OH-DPAT nor RU24969 produced any significant agonist effects in concentrations up to 100 μM. The maximum response produced by 5-CT was $56 \pm 5\%$ of that produced by 5-HT, a difference that was significant ($P < 0{\cdot}05$). The response of the caudal artery to 5-HT was also tested in the presence of 8-OH-DPAT 10 μM. At this concentration, 8-OH-DPAT had no effect on the response to 5-HT (concentration ratio $1{\cdot}1 \pm 0{\cdot}1$). In contrast to the results on the caudal artery, 5-HT, 5-CT, 8-OH-DPAT and RU24969 all produced a concentration-dependent contraction of the isolated fundus preparation (Fig. 2). 5-CT (EC50 $0{\cdot}08 \pm 0{\cdot}003$ μM) and 5-HT (EC50 $0{\cdot}03 \pm 0{\cdot}02$ μM) were both more potent on the fundus than they were on the caudal artery. The potency difference between the two was also less, 5-HT being only 2·5 times more potent than 5-CT, a difference that was not significant. RU24969 (EC50 $0{\cdot}18 \pm 0{\cdot}02$ μM) was approximately one-sixth as potent as 5-HT and also produced a lower maximum response ($40 \pm 7\%$ of the 5-HT maximum, $P < 0{\cdot}05$). The maximum response to 8-OH-DPAT was not significantly different from that achieved by either 5-HT or 5-CT, but it was the least potent of the agonists (8-OH-DPAT EC50 30 ± 18 μM).

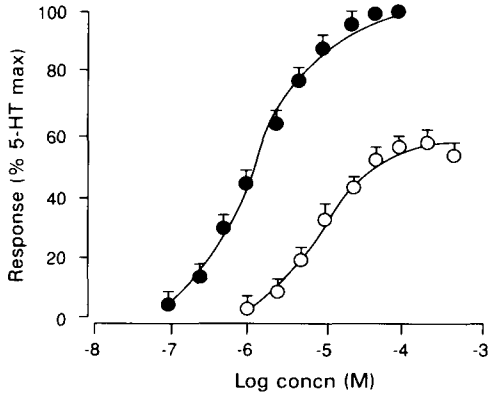

FIG. 1. Contractile effects of 5-HT (●) and 5-CT (○) in the rat caudal artery strip. Maximal responses are compared with that achieved by 5-HT. Each value represents the mean (±s.e.m.) of at least four experiments. 8-OH-DPAT and RU24969 (not shown) were without significant agonist effect up to 100 μM.

The effects of ICI 170,809 on the response of the caudal artery to 5-HT are shown in Fig. 3. ICI 170,809 produced a concentration-related rightward shift of the 5-HT concentration effect curve without having a significant effect on the maximum achievable response. Similar effects were observed

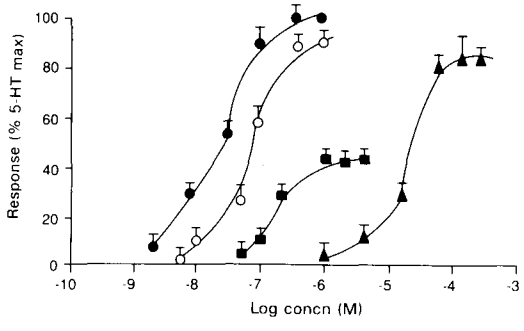

FIG. 2. Contractile effects of 5-HT (●), 5-CT (○), RU24969 (■) and 8-OH-DPAT (▲) in the rat stomach fundus. Maximal responses are compared with that achieved by 5-HT. Each value represents the mean (±s.e.m.) of at least four experiments.

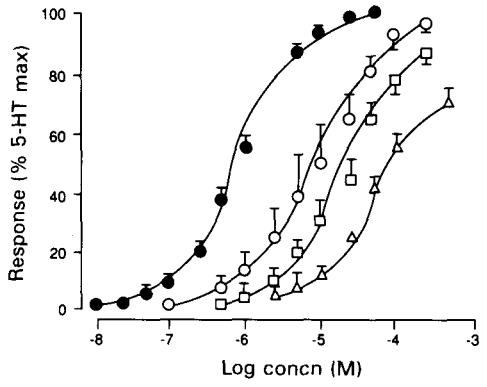

FIG. 3. Antagonist activity of ICI 170,809 in the rat caudal artery. Contractile responses to 5-HT in the absence (●) and presence of 10 nM (○), 50 nM (□) and 100 nM (△) ICI 170,809. Each value represents the mean (±s.e.m.) of at least four experiments.

Table 1. pA_2 values for ICI 170,809, ICI 169,369 and ketanserin vs 5-HT on the rat isolated caudal artery.

Compound	pA_2 (mean ± s.e.m.)	Slope*
ICI 170,809	9·8 ± 0·12	0·75
ICI 169,369	8·2 ± 0·05	1·08
Ketanserin	8·4 ± 0·06	1·09

* In no case was the slope significantly different from unity, n = 4–8.

with ICI 169,369 and ketanserin. Analysis of these data according to the method of Arunlakshana & Schild (1959) indicated that the antagonism was competitive and the results of that analysis are shown in Table 1. The effects of methiothepin and methysergide were also investigated. Methiothepin at 100 nM produced non-surmountable antagonism of 5-HT-induced contractions of the caudal artery. At 100 nM the rightward shift of the 5-HT concentration-effect curve appeared parallel (concentration ratio 7·8 ± 2·8) but the maximum response was reduced by 18 ± 4%. At 100 nM, methiothepin caused a marked depression of the maximum achievable response to 14 ± 5% that of 5-HT on its own ($P < 0·01$). Methysergide had qualitatively similar effects. At 1 nM, the concentration ratio was 6·9 ± 2·3 and the maximum response was reduced by 26 ± 5%. At 100 nM, the maximum was reduced by 65 ± 8% ($P < 0·01$). Ondansetron, at a concentration known to be effective as an antagonist at 5-HT_3 receptors, was without effect on the response of the caudal artery to 5-HT.

The effects of ICI 170,809 on the response of the fundic strip to 5-HT are shown in Fig. 4. In contrast to its effects on the caudal artery ICI 170,809 behaved like a non-surmountable antagonist on this tissue. The maximum response to 5-HT was reduced in a dose-related manner with a concentration of 10 μM reducing the response by 79 ± 1%. ICI 169,369, methysergide and methiothepin behaved in a similar manner to ICI 170,809 and the results are summarized in Table 2, which compares the concentration ratio for the shift in the 5-HT concentration-effect curve and the depression of the maximum response for each of the antagonists. Ketanserin at a concentration of 100 nM had no significant effect on the response of the fundic strip to 5-HT (Fig. 5). Only at 10 μM was there any effect on the response to 5-HT, when there was

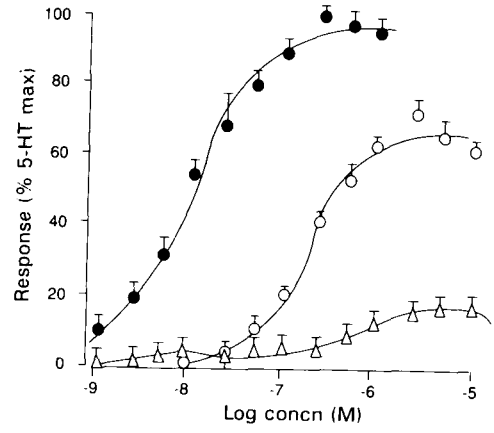

FIG. 4. Antagonist activity of ICI 170,809 in the rat stomach fundus. Contractile responses to 5-HT in the absence (●) and presence of 0·1 (○) and 10 μM (△) ICI 170,809. Each value represents the mean (±s.e.m.) of at least four experiments.

Table 2. Effects of antagonists on the responses to 5-HT in the rat isolated fundic strip.

Compound	Concn (μM)	Concn ratio	Reduction in maximum (%)
ICI 170,809	0·1	37·9 ± 9·8	24 ± 3*
	10·0	NC	79 ± 1**
ICI 169,369	0·1	2·9 ± 0·8	19 ± 3*
	0·5	NC	47 ± 8*
	10·0	NC	80 ± 5**
Methysergide	0·001	1·9 ± 0·4	30 ± 8*
	0·01	NC	80 ± 5**
Methiothepin	0·01	4·5 ± 1·9	32 ± 5*
	0·1	NC	60 ± 8**

* $P < 0·05$, ** $P < 0·01$, n = 4–8. NC = not calculated due to the depression of the maximum response.

weak surmountable antagonism (concentration ratio 8·6 ± 2·7). At this high concentration the shift of the 5-HT responses on the caudal artery would have been about three orders of magnitude. Ondansetron at a concentration of 10 μM had no effect on the response of the fundus to 5-HT.

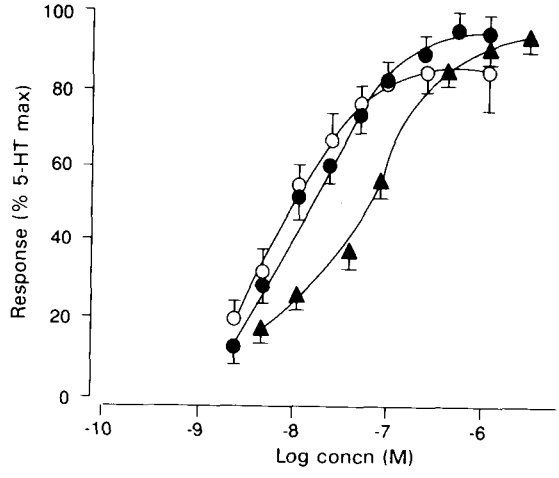

FIG. 5. Contractile responses to 5-HT in the absence (●) and presence of 0·1 (○) and 10 μM (▲) ketanserin in the rat stomach fundus. Each value represents the mean (±s.e.m.) of at least four experiments.

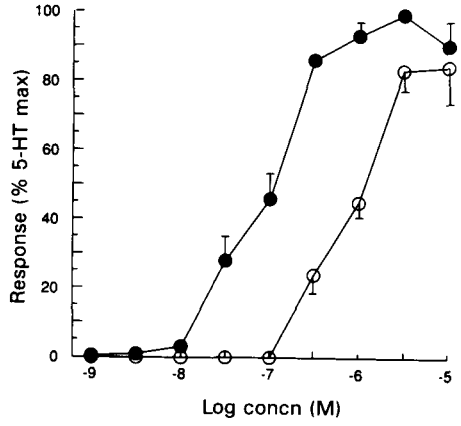

FIG. 6. Contractile responses to 5-HT in the absence (●) and presence of 0·1 μM ICI 170,809 and ketanserin (○) in the rat stomach fundus. Each value represents the mean (±s.e.m.) of at least four experiments.

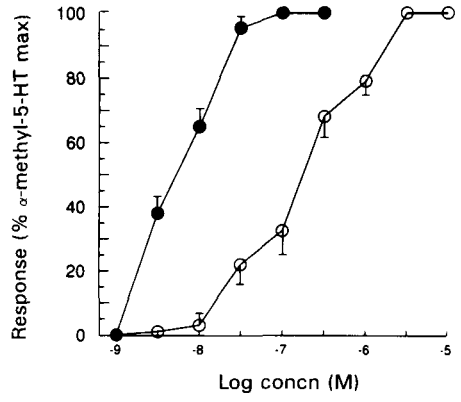

FIG. 8. Contractile responses to α-methyl-5-HT in the absence (●) and presence of 0·1 μM ICI 170,809, cyanopindolol, ketanserin and atropine (○) in the rat stomach fundus. Each value represents the mean (±s.e.m.) of at least four experiments.

The effects of ICI 170,809 on the response of the fundus to 5-HT in the presence of ketanserin 10 μM is shown in Fig. 6. Under these conditions, the effect of ICI 170,809 was not significantly different to that observed when ketanserin was absent from the bathing fluid (Fig. 4). The effect of ICI 170,809 (100 nM) on responses of the fundus to acetylcholine is shown in Fig. 7. At this concentration, ICI 170,809 produced a marked inhibition of the response to 5-HT, but had no effect on the response to acetylcholine.

Concentration-effect for α-methyl-5-HT was studied in the presence of atropine, cyanopindolol and ketanserin, all at a concentration of 1 μM in the Krebs–Henseleit solution. The effects of ICI 170,809 on the response to α-methyl-5-HT under these conditions are shown in Fig. 8. ICI 170,809 (100 nM) produced a parallel rightward shift of the α-methyl-5-HT concentration effect curve with a concentration ratio of 31·4. This would be equivalent to a pA_2 value of 8·5.

Discussion

The results with the agonists clearly indicate that the receptors on the fundus and the caudal artery are different; there was a difference in the order of agonist potency; 5-HT = 5-CT > RU24969 > 8-OH-DPAT on the fundus and 5-HT > 5-CT with the other two agonists inactive on the caudal artery. Since it was possible that these two agonists might be acting as antagonists on the caudal artery (i.e. having affinity for the receptor, but no efficacy), 8-OH-DPAT was tested at the high concentration of 10 μM for its ability to antagonize 5-HT. 8-OH-DPAT was ineffective as an antagonist, indicating that it has no affinity for the 5-HT_2 receptor.

A characteristic of the 5-HT_2 receptor is that 5-HT itself has a relatively low potency compared with its potency at 5-HT_1 receptors (Bradley et al 1986). Such a potency difference was observed in the present experiments, since 5-HT was more potent on the fundus (pD50 = 7·5) than on the caudal artery (pD50 = 6·1). The greater potency of 5-HT over 5-CT is also consistent with the view that the caudal artery receptor is a 5-HT_2 receptor (Feniuk 1984). Using similar reasoning, the receptor on the fundus would seem likely to be of the 5-HT_1 group, since 5-CT is of a similar potency to 5-HT (Humphrey 1984). Although the 5-HT_{1A} agonist 8-OH-DPAT (Middlemiss & Fozard 1983) had the same efficacy as 5-HT on the fundus, it was very weak. Therefore, it would seem unlikely that the fundic 5-HT receptor is of this particular subtype. The 5-HT-induced contractions of the guinea-pig ileum have an indirect component due to the release of acetylcholine (Gaddum & Picarelli 1957). The possibility of such a component being involved in the response of the fundus was eliminated by having atropine present throughout the experiments and therefore the effects of the agonists are most likely to be due to a direct action on the smooth muscle.

The ability of agonists to aid in the discrimination between receptor subtypes is limited and therefore a series of experiments was carried out using a number of antagonist drugs. Ketanserin, ICI 169,369 and ICI 170,809 were potent and competitive antagonists of 5-HT on the caudal artery. All three antagonists have high affinity for 5-HT_2 binding sites, but they also display some affinity for 5-HT_{1C} sites (Major et al unpublished data). However, the study by Major et al showed that the two ICI compounds had almost the same affinity for 5-HT_2 and 5-HT_{1C} sites, whereas ketanserin

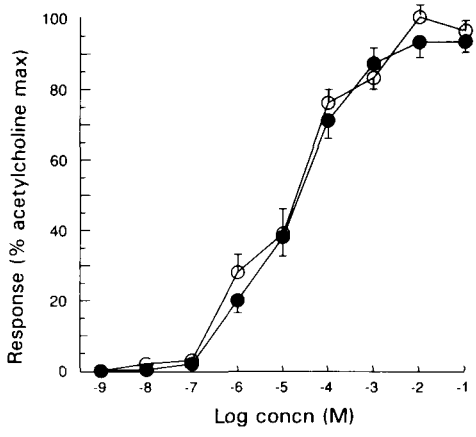

FIG. 7. Contractile responses to acetylcholine in the absence (●) and presence of 0·1 μM ICI 170,809 (○) in the rat stomach fundus. Each value represents the mean (±s.e.m.) of at least four experiments.

had less than one-hundredth the potency at the 5-HT_{1C} site. Thus the results with ketanserin and the novel ICI compounds are consistent with the view that the receptor on the caudal artery is a 5-HT_2 receptor. Methiothepin and methysergide were also used as antagonists on the caudal artery. Both compounds have affinity for the 5-HT_2 receptor subtype (Bradley et al 1986), but they also have affinity for many of the other subtypes of the 5-HT receptor (Bradley et al 1986). Therefore, these drugs are not useful as tools to indicate the receptor subtype involved. However, as discussed below, it was hoped that they might point to differences between the receptors on the caudal artery and fundus. For the sake of completeness, the possibility that 5-HT_3 receptors were involved in the response on the caudal artery was eliminated by demonstrating that ondansetron, at a concentration known to antagonize 5-HT_3 receptors (Fozard 1989), was without effect.

The first and very clear point of difference between the caudal artery and the fundus came with the experiment involving ketanserin. At 0·1 μM, a concentration that would have produced a tenfold shift on the caudal artery, ketanserin was without effect on the response to 5-HT in the fundus. Even at a concentration that would produce a thousandfold shift on the caudal artery (10 μM) the effect on the fundus was only about tenfold. Thus, these results indicate that the fundic receptor is not 5-HT_2 and do not confirm earlier claims that this was the case (Gregg & Osbourne 1985). The difference in potency for ketanserin on the caudal artery vs the fundus is of the order of 100 and it is interesting that this is the same value as that obtained when ketanserin is compared for its affinity for 5-HT_2 and 5-HT_{1C} binding sites, the IC50 values being 3·2 and 333 nM, respectively (Major et al unpublished data). Thus, the evidence with ketanserin suggests that the 5-HT receptor on the fundus could be 5-HT_{1C}. If this were the case, then the two ICI compounds ought to antagonize 5-HT on the fundus and have a similar potency to that on the caudal artery. Unfortunately, interpretation of the results with ICI 169,369 and ICI 170,809 was complicated by the fact that they behaved as non-surmountable antagonists. The non-surmountable antagonism raised the possibility that the ICI compounds were non-selective antagonists on this tissue, but this was shown not to be the case since ICI 170,809 did not block responses to acetylcholine. In addition, 5-HT_3 receptors would not appear to be involved in the response of the fundus to 5-HT since a high concentration of the 5-HT_3 antagonist, ondansetron, was ineffective.

The present results, therefore, clearly demonstrate that the response of the fundus to 5-HT is not mediated by either 5-HT_2 or 5-HT_3 receptors. The most likely receptor involved, considering the known pharmacology of the ICI compounds (Major et al unpublished data), is the 5-HT_{1C} subtype. However, there is some evidence not consistent with this view. Baez et al (1990) found that the 5-$HT_{2/1C}$ antagonists, LY5387 and ritanserin were non-competitive antagonists of 5-HT on the rat fundus, but that their potency was less than would be expected from their affinity for 5-HT_{1C} binding sites, a situation analogous to our findings with ICI 169,369 and ICI 170,809. Further, Baez et al (1990) were unable to detect hybridization of a 5-HT_{1C} receptor cDNA probe with any mRNA from the rat stomach fundus. Indeed, Kalkman & Fozard (1991) consider the fundus 5-HT receptor to bear greatest resemblance to the 5-HT_{1D} recognition site. Therefore, in order to explore further the pharmacology of the fundus, we decided to use α-methyl-5-HT, an agonist claimed to have affinity for the 5-HT_2-receptor subtype (Fozard 1987) in the presence of atropine, to block muscarinic receptors, cyanopindolol to block 5-$HT_{1A/B}$ receptors (Fozard 1987) and ketanserin to block 5-HT_2 receptors (Van Neuten et al 1981). Under these conditions ICI 170,809 produced a parallel rightward shift of the α-methyl-5-HT concentration-response curve without any change in the maximum achievable response (Fig. 8). The calculated pA_2 value, based on this single concentration of ICI 170,809, was 8·5 which was significantly different ($P<0·01$) from that obtained from the 5-HT_2 receptor.

Molecular biology studies have shown that the 5-HT_{1C} receptor has more in common with the 5-HT_2 receptor than any of the other 5-HT receptors that have been identified (Hartig 1989). More recent studies (Foquet et al 1992a, b) have used a probe derived from the 5-HT_{1C} receptor sequence and have shown that it hybridizes to an additional gene called 5-HT-receptor like. This gene appears to encode the stomach 5-HT receptor and has much in common with both the genes for the 5-HT_2 and 5-HT_{1C} receptors. Indeed, there is a case for reclassifying the 5-HT_{1C} receptor as a 5-HT_2 variant. The pharmacological characteristics that we have demonstrated in this study are consistent with the view that the fundus receptor bears a closer resemblance to these two receptors than any of the other receptors that have been described previously.

Since this paper was accepted for publication Humphrey et al (1993) have basically stated the same argument used here, i.e., that the 5-HT-receptor subtype in the rat fundus bears greater similarity to the 5-HT_2 subtype than to any of the other subtypes identified.

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